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ORIGINAL ARTICLE

Intima-media thickness in secondary anti-phospholipid syndrome patients: Impact of disease activity

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KEYWORDS

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Abstract *Aim of the work:* To assess the carotid intima-media thickness (IMT) and plaque formation in systemic lupus erythematosus (SLE) patients with and without antiphospholipid syndrome (APS) by doppler ultrasonography and to correlate it with the clinical features, disease activity and damage.

Patients and methods: Thirty-six female SLE patients with secondary APS and another 36 without were included. Thirty-six matching healthy volunteers were included as control. In patients, the disease activity and damage were assessed using the SLE Disease Activity Index (SLEDAI) and Systemic Lupus International Collaborating Clinics (SLICC) index, respectively. Doppler ultrasound was carried out for patients and control and the IMT was measured.

Results: The demographic and clinical characteristics of patients are presented. The disease activity was significantly higher in SLE patients with APS (19.7 ± 7.9) compared to SLE only patients (15.1 ± 9.2) ($p = 0.03$). The low density lipoprotein (LDL) was significantly increased in APS patients ($p = 0.04$). The IMT was comparable between both groups (0.83 ± 0.15 mm) vs (0.86 ± 0.2 mm) ($p = 0.55$) and both were significantly increased compared to the control (0.61 ± 0.11 mm) ($p < 0.0001$). The dyslipidemia present in the patients showed a significant difference in the measured lipid profile parameters ($p < 0.0001$). The IMT significantly correlated with the SLEDAI in both groups ($p < 0.002$ and < 0.001 respectively).

Conclusion: The increased IMT as a marker of atherosclerosis is confirmed in SLE patients with no obvious difference in those with secondary APS. The link between the increased IMT and disease activity favors the role of disease-specific potential risk factors, in addition to the traditional conventional ones, in the development of atherosclerosis.

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic and multisystemic autoimmune disorder [1,2]. It may result from disturbed tolerance to self antigens and development of auto-antibodies leading to the formation of immune complexes. These immune deposits in the tissues initiate an inflammatory response by activating the complement cascade and recruiting inflammatory cells [3,4]. The defective clearance of apoptotic cells [5]; increased oxidative stress [6] and gene polymorphism [7] are believed to be among the multiple causes of SLE. Despite improved prognosis, SLE patients remain at increased risk for early death as vascular events occur with increased frequency [8].

The most common cause of death in SLE patients affected by disease for more than 5 years is cardiovascular disease (CVD) [2,9]. The IMT has been found to be increased in many rheumatic diseases such as rheumatoid arthritis [10], SLE [11,12], Behcets disease [13] and osteoarthritis [14]. Together with classical conventional risk factors, other mechanisms (disease-specific factors) promote accelerated atherosclerosis in SLE. Traditional CVD risk factors include age, hypertension, diabetes mellitus, dyslipidemia, previous vascular event, menopause and smoking. The nontraditional factors include lupus nephritis (LN), presence of pro-inflammatory cytokines, inflammatory mediators, antiphospholipid (APL) antibodies and corticosteroid use [2]. Recent evidence strongly suggests that atherosclerotic plaque is largely driven by inflammation and an active immunological response, in contrast to the long-held belief that plaque is a passive accumulation of lipids in the arterial wall [9].

The antiphospholipid syndrome (APS) was first described in the early 1980s. The term was coined to describe patients presenting with recurrent arterial and venous thrombosis or pregnancy complications. It was first reported in SLE patients, but later on it became obvious that SLE is not a necessary condition for its occurrence. Antibodies to phospholipids were found to play a central role in the disease, hence its name. The main hindrance to an accurate diagnosis was the lack of standardized antiphospholipid (APL) antibody testing and lately a combination of tests has been acknowledged [15]. The role of APL antibodies in atherosclerosis development in SLE remains unclear [16].

The aim of the present study was to assess the carotid intima-media thickness (IMT) and plaque formation in SLE patients with and without APS by Doppler ultrasonography (US) and to correlate it with the clinical features, disease activity and damage.

2. Patients and methods

Thirty-six female SLE patients with definite secondary APS diagnosed according to the International consensus statement on classification criteria [17] were recruited. Another 36 female SLE patients without APS were also included. All patients fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE [18] and were recruited from the Rheumatology and Internal medicine out-patient Clinics of Cairo University Hospitals. Thirty-six age and sex matched healthy volunteers were included as a control group.

Full history taking, thorough clinical examination and relevant laboratory investigations were performed for all the patients. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [19] while assessment of organ damage was made using the Systemic Lupus International Collaborating Clinics/ACR (SLICC/ACR) index [20].

Doppler ultrasound scan was carried out for patients and control. The intima-media thickness (IMT) measurements on each side were taken at the common carotid artery (CCA) (10 mm before and 5–10 mm cranially to the start of the bulb) and the internal carotid artery 10 mm after the flow divider. For each patient the highest IMT among the measured segments studied on each side was recorded and the mean value calculated. According to current sonographic criteria the IMT was considered "normal" when less than 0.9 mm, "thickened" when the IMT was equal to or more than 0.9 mm and when the thickness was more than 1.3 mm was indicative of atherosclerotic plaque [21].

The study was in accordance to the ethical standards of the Helsinki declaration. Informed consent was obtained from all participants prior to the study.

Statistical analysis: Statistical Package for Social Science (SPSS) program version 15 was used for analysis of data. Data were presented as mean ± SD. Mann–Whitney test was used for the comparison analysis of two non-parametric quantitative and Chi square test for qualitative variables. The one way ANOVA was used to compare more than 2 groups. Spearman′s correlation was used for the detection of the relation between two non-parametric variables. p-Value was considered significant if < 0.05.

3. Results

The study included 72 SLE female patients divided into 2 groups according to the presence of secondary APS. The demographic and clinical characteristics of patients are presented in Table 1. None of the patients was menopausal or smoking. None of the patients was diabetic. All patients were receiving oral corticosteroids and cyclophosphamide was received in 18 SLE patients and in 15 with APS. The study included 36 age and sex matched healthy controls with a mean age of 28.1 ± 5.7 years. The body mass index (26.2 ± 3.02) was also comparable to patients.

The risk factors for atherosclerosis and IMT are presented in Table 2. The lipid profile of the control showed; cholesterol (124.2 ± 40.6 mg/dl), triglycerides (92.5 ± 30.8 mg/dl), high density lipoprotein (HDL) (67.4 ± 14.4 mg/dl) and low density lipoprotein (LDL) (53.6 ± 7.4 mg/dl). The dyslipidemia present in the patients showed a significant difference in the values of the measured lipid profile parameters ($p < 0.0001$).

The IMT in the control was 0.61 ± 0.11 mm and the thickness was significantly increased in patients (< 0.0001) (Fig. 1). In SLE patients with APS there was an increased IMT found in 18 (50%) and none had plaques while in the SLE only patients, 14 (38.9%) had an increased IMT of which 3 had plaques. The medications received had no effect on the IMT.

Correlations of the IMT in SLE patients with and without APS are presented in Table 3. On regression analysis , in SLE patients with secondary APS, all the variables including the age, disease duration, lipid profile, urinary protein, SLEDAI and SLICC were predictors of the IMT ($p < 0.0001$); while

Table 1 Demographic and clinical characteristics of systemic lupus erythematosus patients.

Characteristic	SLE + APS (36)	SLE (36)	*p*
Age (years)	29.0 ± 6.8	27.9 ± 6.9	0.5
Disease duration (years)	7.1 ± 6.3	4.1 ± 2.6	**0.01**
ESR (mm/1st h)	60.7 ± 36.8	59.3 ± 23.7	0.86
Serum creatinine (mg/dl)	0.73 ± 0.25	0.85 ± 0.3	0.51
24 h urine protein	0.88 ± 0.81	1.1 ± 1.5	0.44
Anti-DNA positivity	21 (58.3)	27 (75)	0.14
Anti-Ro positivity	12 (33.3)	14 (38.9)	0.39
Steroid dose (mg/day)	21.9 ± 6.5	24.5 ± 12.2	0.26
Manifestations			
Pulmonary	12 (33.3)	21 (58.3)	**0.03**
Cardiac	6 (16.7)	4 (11.1)	0.5
Renal	18 (50)	25 (69.4)	0.1
Neuropsychiatric	18 (50)	15 (41.7)	0.49
Arthritis	12 (33.3)	13 (36.1)	0.81
Indices			
SLEDAI	19.7 ± 7.9	15.1 ± 9.2	**0.03**
SLICC	2.5 ± 1.8	1.9 ± 2.2	0.18

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, SLICC: Systemic Lupus International Collaborating Clinics. Results are presented as mean ± SD or *N* (%). Bold values indicate a signficant difference.

Table 2 Risk factors for atherosclerosis and IMT of the systemic lupus erythematosus patients.

Factor	SLE + APS (36)	SLE (36)	*p*
Body mass index (BMI)	27.7 ± 3.8	25.7 ± 2.4	0.5
Hypertension *N* (%)	12 (33.3)	15 (41.7)	0.47
Cholesterol (mg/dl)	222.7 ± 49.9	224.8 ± 53.7	0.86
Triglycerides (mg/dl)	207.7 ± 74.4	184.7 ± 76.6	0.2
HDL (mg/dl)	42.6 ± 10.7	43.4 ± 12.6	0.76
LDL (mg/dl)	161.3 ± 36.4	141.8 ± 42.6	**0.04**
IMT (mm)	0.83 ± 0.15	0.86 ± 0.2	0.55

HDL: high density lipoprotein, LDL: low density lipoprotein, IMT: intima-media thickness. Results are presented as mean ± SD or *N* (%). Bold values indicate a signficant difference.

in those with SLE only, the SLEDAI and triglycerides were significant risk factors (p0.012 and p0.047 respectively).

4. Discussion

Systemic lupus erythematosus is known to be one of the strongest risk factors for atherosclerosis. Patients with SLE have an excess cardiovascular risk compared with general population, leading to increased cardiovascular morbidity and mortality. Although the precise explanation for this is yet to be established, it seems to be associated with the presence of an accelerated atherosclerotic process, arising from the combination of traditional and lupus-specific risk factors [1]. The CVD risk among SLE patients compared with the general population is at least doubled. While older SLE patients appear to have the highest absolute risks of CVD, young women have alarmingly high relative risks. Both traditional and SLE-specific risk factors are important, although there are discrepancies within

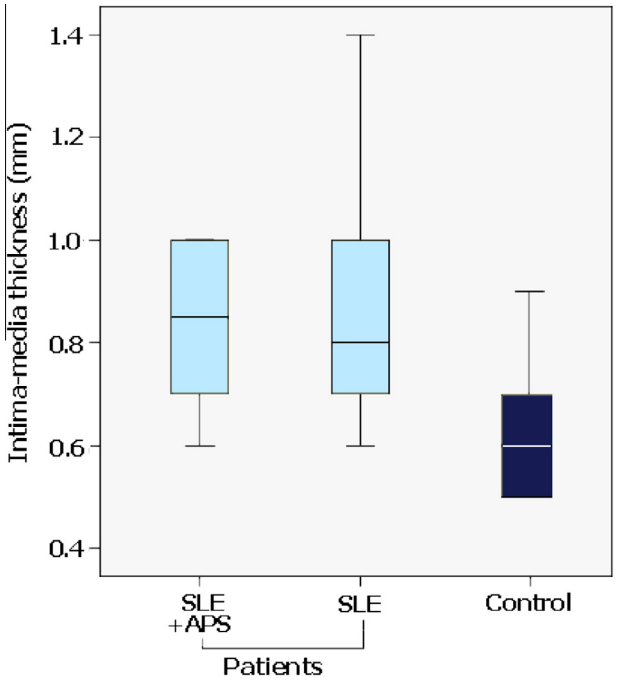

Fig. 1 The intima-media thickness in systemic lupus erythematosus patients with and without antiphospholipid syndrome and the control.

Table 3 Correlation of the intima-media thickness in SLE patients with and without antiphospholipid syndrome with different parameters.

Parameter	Intima-media thickness (mm)	
	SLE + APS	SLE
Age (years)	0.64 (**< 0.001**)	0.22 (0.20)
Disease duration (years)	0.11 (0.54)	0.08 (0.67)
Body mass index	0.16 (0.36)	0.40 (0.60)
Cholesterol (mg/dl)	0.24 (0.17)	0.25 (0.14)
Triglycerides (mg/dl)	−0.14 (0.4)	0.43 (**0.009**)
HDL (mg/dl)	−0.34 (**0.046**)	−0.27 (0.11)
LDL (mg/dl)	−0.02 (0.9)	0.22 (0.19)
Urinary protein (g/24 h)	0.27 (0.12)	0.33 (0.053)
Creatinine (mg/dl)	0.50 (0.10)	0.78 (0.23)
Anti-dsDNA	0.40 (**0.02**)	0.17 (0.32)
Steroid dose (mg/day)	0.14 (0.43)	0.15 (0.38)
SLEDAI	0.49 (**0.002**)	0.59 (**< 0.001**)
SLICC	−0.13 (0.46)	0.30 (0.08)

HDL: high density lipoprotein, LDL: low density lipoprotein, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, SLICC: Systemic Lupus International Collaborating Clinics. Bold values indicate a signficant difference.

the literature [22,23]. Traditional risk factors do not fully explain this increased risk of CVD thus strongly suggesting that autoimmunity contributes to accelerated atherosclerosis. Altered immune system function is recognized as the primary contributor to both the initiation and progression of atherosclerosis. Multiple manifestations of autoimmunity, including changes in cytokine levels and innate immune responses, autoantibodies, adipokines, dysfunctional lipids and oxidative stress, could heighten the atherosclerotic risk. SLE-specific

CVD risk factors are beginning to be discovered and development of a comprehensive, clinically feasible biomarker panel could be invaluable for the identification and treatment of patients at risk of developing accelerated atherosclerosis [23].

The increased IMT in SLE in the present study has been confirmed in several studies [24–26]. Furthermore, in other studies on Egyptian SLE patients, the IMT was found to be significantly increased [11,12,27].

In the present study, the significant correlation of the IMT with the disease activity in all SLE may throw light on the possible role of inflammation in determining the thickness of the intima-media in SLE patients with or without APS and should be considered among the risk factors and not just the traditional atherosclerotic factors. In those patients with APS, there was a significant correlation of the IMT with the anti-DNA positivity. In other recent studies, the SLEDAI was significantly associated with carotid IMT [11,28]. In the study of Shang et al. [30] the patients with active disease (SLEDAI $\geqslant$ 3) had significantly higher carotid augmentation index (CAI) than inactive ones. After making adjustments for age, body mass index (BMI) and blood pressure, carotid AI rather than the IMT was found to significantly correlate with the SLEDAI. They concluded that SLE was an independent risk factor of sub-clinical atherosclerosis and arterial stiffness may identify the presence of active disease. Furthermore, in a follow-up study, there was no significant association between SLEDAI, anti-dsDNA and anti-phospholipid with the progression of subclinical atherosclerosis [31].

In the present study, there was no significant difference in the frequency of increased IMT in SLE patients with or without APS. It has been reported that the role of antiphospholipid (APL) antibodies in premature CVD remains a matter of debate. β2-Glycoprotein I, abundantly found in vascular plaques, has been hypothesized to be protective against atherosclerosis development. Antibodies against this molecule could, in theory, be detrimental to the vessel wall and promote the activation of inflammatory cascades by immune-complex formation. However, it has been found that early markers of CVD risk were not different compared with age and gender matched healthy controls [16]. Previous studies showed that the presence of APL antibodies did not correlate with endothelial dysfunction or carotid IMT in SLE [16,32,33].

In the present study, LDL was significantly higher in SLE patients with APS compared to those without. Furthermore, there was a significant correlation of the IMT with the triglycerides in SLE only patients and negatively with HDL in those patients with APS. Even though APS and atherosclerosis share several similar features as increased levels of antibodies to oxidized low density lipoprotein (oxLDL) and phospholipids, endothelial dysfunction, platelet activation and thrombus formation, increased oxidative stress and immune cell activation, the epidemiologic evidence that the presence of APL Abs may be a serologic marker or an independent risk factor for atherosclerosis is inconclusive [34–36]. Accelerated atherosclerosis is considered a leading cause of morbidity and mortality in SLE which confirms the importance of recognizing and controlling modifiable risk factors, even in asymptomatic patients [37]. Hypercholesterolemia increases the risk of clinical or subclinical atherosclerosis in SLE. Established risk factors are important, but do not fully explain the increased frequency of atherosclerosis in SLE and its cause is likely to be multifactorial [38,39]. Furthermore, it has been suggested that SLE is independently associated with accelerated atherosclerosis [40]. Current approaches to the prevention of atherosclerosis in SLE involve targeting modifiable cardiac risk factors. Future preventive strategies may include therapies that counteract the immunologic responses that lead to plaque formation [9].

Antiphospholipid syndrome (APS) is the most frequent cause of venous and arterial thrombotic events in young patients. The accelerated atherosclerosis in APS is linked-to the underlying associated systemic autoimmune diseases, in particular, SLE. However, as arterial ischemic events can occur in primary APS – with no other systemic disorders – even in the absence of traditional cardiovascular risk factors and overt atherosclerosis, this finding speaks in favor of pro-coagulant activity of APL antibodies rather than for their role in atherosclerotic plaque formation [41]. The link between immune and inflammatory responses in the pathogenesis of CVD has been firmly established; yet, despite our increasing knowledge, accelerated atherosclerosis continues to be a significant co-morbidity and cause of mortality in SLE [42].

In the present study, plaques were not found in those patients with APS but were found in 3 (8.3%) of SLE only cases. Patients in this study were of relatively young age. It has been reported that carotid plaque can be detected in 21% of SLE patients under the age of 35 years and in up to 100% of those over the age of 65 years [16]. In another study on Egyptian SLE patients, subclinical carotid plaque was found in only 5% of the patients [12]. In another study on SLE and the risk of carotid atherosclerosis, 50% of the patients had carotid plaque [43].

Cardiovascular disease is a major complication of lupus and a leading cause of death. Additional studies are needed in order to identify the most effective preventive strategies and most predictive vascular risk biomarkers [44]. No obvious effect was detected of the medications received in the present study on the IMT. It has been reported that multiple SLE therapeutics seem to affect the development and progression of atherosclerosis both positively and negatively [23]. Development and establishment of new stratification tools to efficiently identify patients at increased cardiovascular risk are essential. With advances in imaging techniques, the ultimate goal of cardiovascular assessment will shift from assessing symptomatic patients to diagnosing asymptomatic early CVD which will hopefully help prevent its progression [1].

Details of autoantibodies involved in APS should be considered in further studies in order to assess their role in the risk of atherosclerosis in this subset of SLE patients. A study on a larger number of patients and preferentially a longitudinally designed one is recommended in future work. Extending the study to include patients with primary APS may help to elucidate the role of the disease or its autoantibodies in the prediction of atherosclerosis.

In conclusion, the increased IMT as a marker of atherosclerosis is confirmed in SLE patients with no obvious difference in those with secondary APS. The link between the increased IMT and the disease activity suggests the role of disease-specific potential risk factors, in addition to the traditional conventional ones, in the development of atherosclerosis.

Conflict of interest

None.

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